

Synthesis of the new carbohydrate Ibuprofen ester as possible prodrug

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Abstract:

Synthesis of new ibuprofen ester (5) is described . Ester formation was achieved by esterification of the ibuprofen carboxylic acid (1) with diacetone fructose (3) The structure of synthesized compounds were characterized by means of FTIR and UV, Preliminary results showed that the prepared fructose-drug conjugates underwent hydrolysis and released the pound ibuprofen and fructose. However, detailed kinetic studies of chemical and potential enzyme hydrolysis still remain to be down.

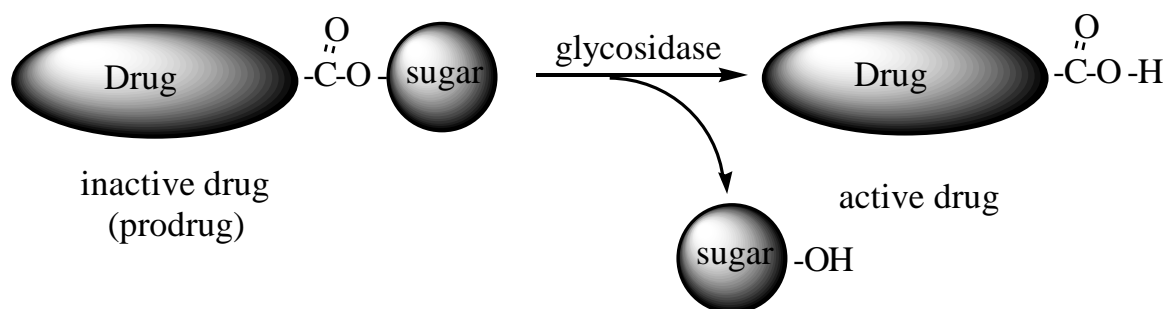
الخلاصة:

يتضمن البحث تحضير مشتق استري جديد لدواء الايبوبروفين يكون فيها جذر الاستر سكر الفركتوز وذلك بتحويل مجموعة الحامض للايبوبروفين إلى كلوريد الحامض ثم ادخاله بتفاعل أسترة مباشرة مع مجموعة الكحول لسكر الفركتوز المحمي في الموقع رقم 1 لزيادة كل من الذوبانية و الامتصاصية للايبوبروفين مما يمكن من تقليل كمية الدواء المعطى للمريض والتقليل من اعراضه الجانبية , تم تشخيص المركبات المحظرة بواسطة طيف الأشعة تحت الحمراء والأشعة فوق البنفسجية وكانت النتائج مطابقة لما هو متوقع.

INTRODUCTION

The term "prodrug" or "proagent" was first introduced by Albert¹ to signify pharmacologically inactive chemical derivatives that could be used to alter the physicochemical properties of drugs, in a temporary manner, to increase their usefulness and/or to decrease associated toxicity. Since Albert discussed the concept of prodrugs in the late 1950s, the use of the term implies a covalent link between a drug and a chemical moiety, though some authors also use it to characterize some forms of salts of the active drug molecule. Although there is no strict universal definition for a prodrug itself, and the definition may vary from author to author, generally prodrugs can be defined as pharmacologically inert chemical derivatives that can be converted in vivo to the active drug molecules, enzymatically or nonenzymatically, to exert a therapeutic effect. Ideally, the prodrug should be converted to the original drug as soon as the goal is achieved, followed by the subsequent rapid elimination of the released derivatizing group²⁻⁴.

Carbohydrate-drug conjugates connected by potentially metabolisable sacrificial linkages, such as esters, have high potential utility as prodrugs in which the glycan moiety affords both protection and specific transport properties⁵.



This prodrugs have been prepared to increase the bioavailability⁶, solubility⁷, activity⁸, and the selectivity^{9,10}. Ibuprofen , apotent nonsteroidal anti-inflammatory drug, has been

widely used in the treatment of pain and inflammation.^{11,12} Unfortunately, like other nonsteroidal anti-inflammatory agents, ibuprofen carries some side effects such as gastrointestinal irritation^{13,14}. Therefore, the ester prodrugs of ibuprofen were synthesized with the intention of reducing the side effects^{15,16}. It is known that some carbohydrate ester pro-drugs have antibiotic activity. In the light of these results, I aimed to develop carbamate-linked sugars (fructose) with ibuprofen because this linkage is stable in aqueous solution and could be hydrolyzed by glycosidases¹⁷ and no other toxic groups are released from the linkage portion of the molecule, also this may reduce the side effects of ibuprofen and increase the tissue distribution.

EXPERIMENTAL

Melting points were determined on Buch, 510 melting point apparatus and remained uncorrected. Infrared (FTIR) spectra were recorded on a Beckman I. R-8 spectrophotometer. UV spectra were carried out using an Hp 845 2A diode array spectrophotometer, and the wave numbers reported are referenced to the 200 nm cm⁻¹ of chloroform. TLC was performed on silica gel plates kieselgel 60 F245 (Merck, Germany) and the following solvents and solvent mixtures were used: CH₂Cl₂: CH₃OH, CH₂OH, C₆H₆ (2:10), EtOA: CH₃OH (1:5), EtOA: CH₃OH (5:1). Spots were visualized by short-wave UV light and iodine vapor. Column chromatography was performed on silica gel eluent with chloroform. Ibuprofen anhydrous was supplied from Samarra drug industries Samarra, Iraq, the purity of this compound is checked according to m.p and Meric index. All solvents were distilled and dried prior to use. Pyridine was refluxed with K₂CO₃ for 5 h. then fractional distillation over anhydrous K₂CO₃, glass ware was dried overnight in an oven at 130⁰ C and cooled in a desiccator over anhydrous CaCl₂ or silica gel.

General procedure for the compounds synthesis

2, 3 : 4, 5 -di-O-isopropylidene-β-D fructopyranose (3) .

Compound (3) was synthesized from β-D-fructose in acetone following the published procedure.¹⁸

Ibuprofenoyl chloride (2).

Dry powdered ibuprofen (1 gm, 5 mmol) was placed in a distillation flask, redistilled thionyl chloride was added. The mixture was then refluxed with shaking for 3 h., the flask, was cooled the condenser detached and the flask was heated carefully over the hot plate at 60⁰ C with occasional shaking for 20 minutes.

1-diacetone fructosyl ibuprofen ester (4)

Compound (3) (1 gm, 3.8 mmol) was dissolved in anhydrous pyridine (10 mL), ibuprofen chloride (2) (0.85 gm, 3.8 mmol) was added, stirred for 24 h. at room temperature, a mixture of water-chloroform (30 mL) (1:2), filtered and the organic layer was separated, washed with water dried over MgSO₄, filtered, evaporation under reduced pressure.

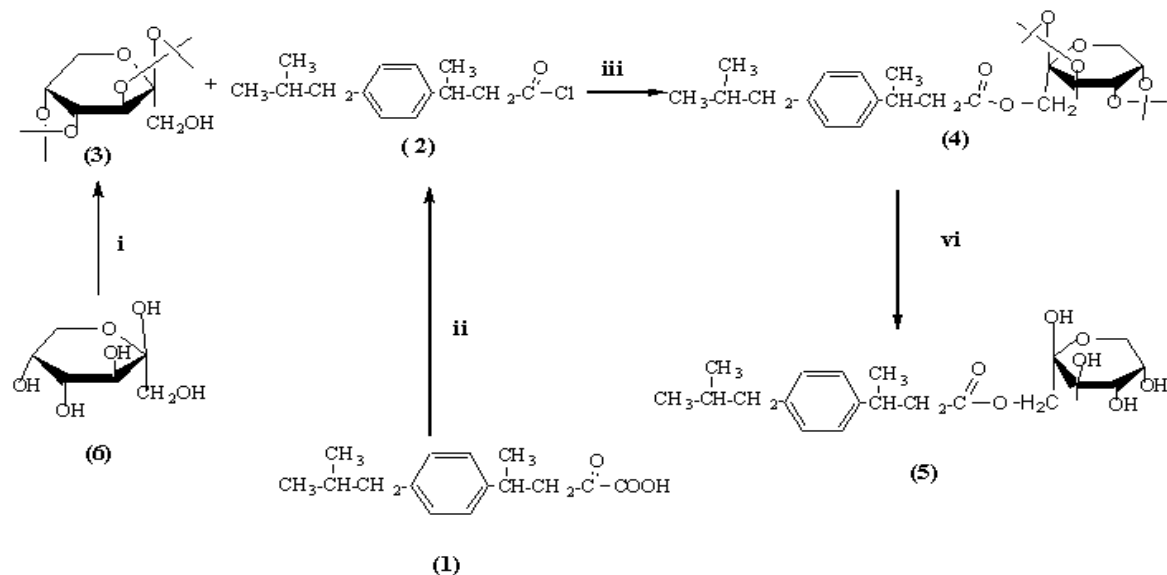
1-fructocyl ibuprofen ester (5).

Compound (4) (1 gm, 2.3 mmol) was dissolved in 10 mL of chloroform, then stirring with 0.5 N (HCl) for 3 h. at 25⁰ C.

RESULTS:

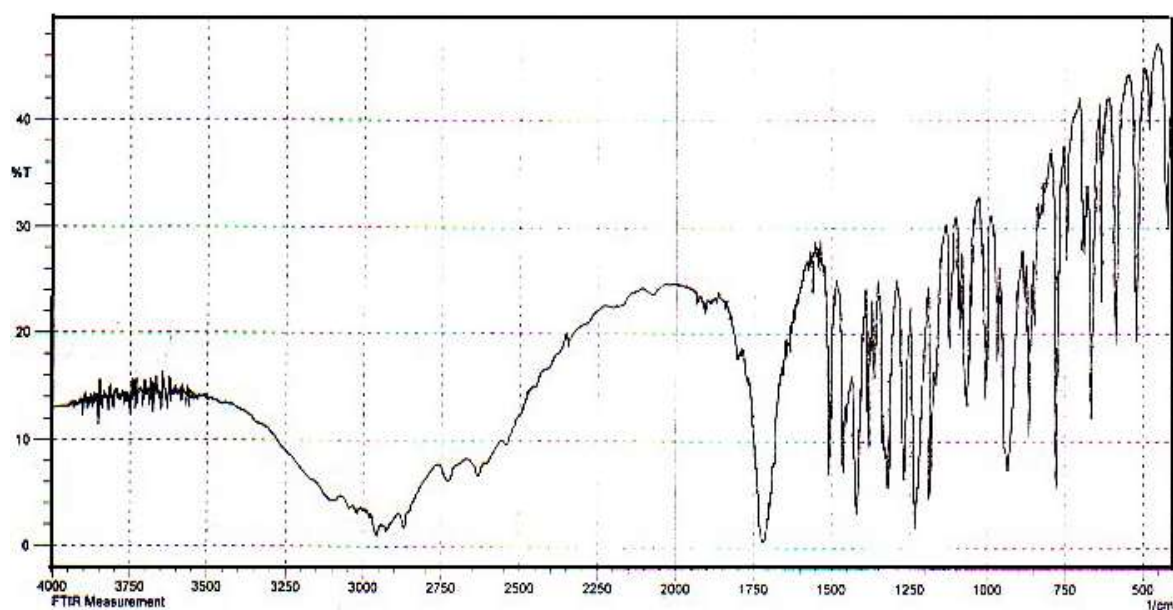
In this paper, a new and convenient method of ibuprofen ester preparation via β-D-fructose was reported. In the first step, carboxylic acid group of ibuprofen was converted to its chloride (2) by reaction with dry thionyl chloride in 45.4% yield, then reacted with 2,3:4,5-di-O-isopropylidene-β-D-fructopyranose (3). 1-diacetone fructocyl ibuprofen ester (4) was formed, then

stirring with 0.5 N of HCl giving the corresponding ester in 50 % (Scheme 1). The following compounds were synthesized: (2),(3), (4) and (5). All except (3), are new compounds. Compound (3) was previously synthesised, but the literature report¹⁸ gave no spectroscopic characterisation. Therefore , its spectroscopic data are reported here, together with the data for the new compounds.



Schem1 : i) acetone , 36 C °, FeCl₃, 10 h. : ii) SOCl₂, 60 C°, 3 hr. : iii) pyridine, 25° C 24 hr. : vi) (0.5 N) HCl , 6 h.

The ester preparation proceeded in mild condition, at room temperature spectral assignment of all synthesized confirmed their structures. FTIR spectra of (5) showed the characteristic absorption bands for OH at ν 3400 , ν C-H aliphatic at 2800 , ν C=O ester 1739. The parallel display of FTIR spectra of ibuprofen (1), ibuprofen chloride (2) , 1-diacetone fructosyl ibuprofen ester (4). and 1-fructocyl ibuprofen ester (5) is presented in (Figure 1,2). Reaction conditions, yields, physical, FTIR spectroscopic, UV and R_f are given in (Table 1).



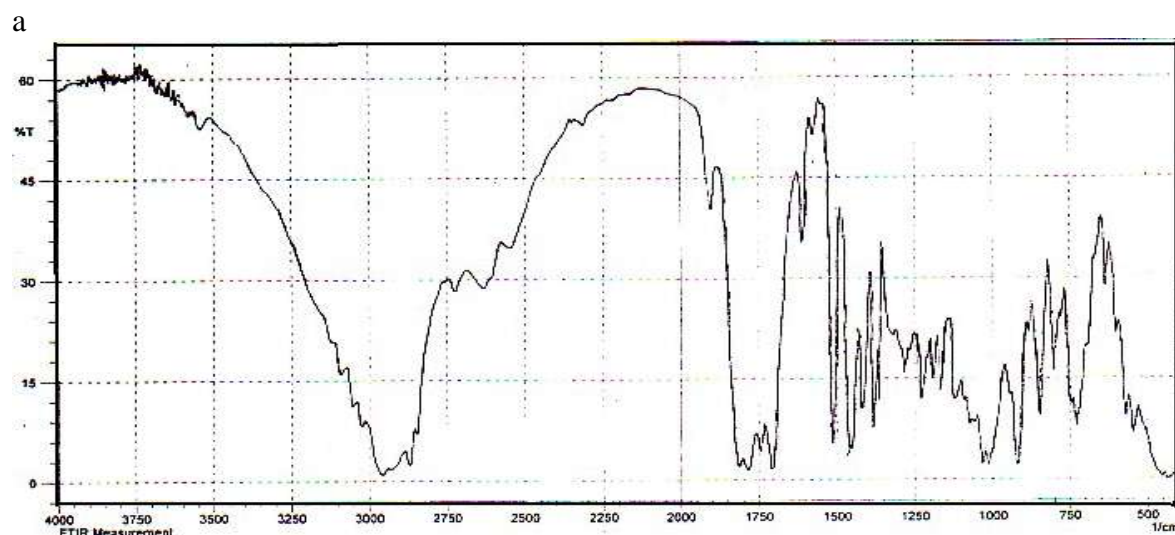
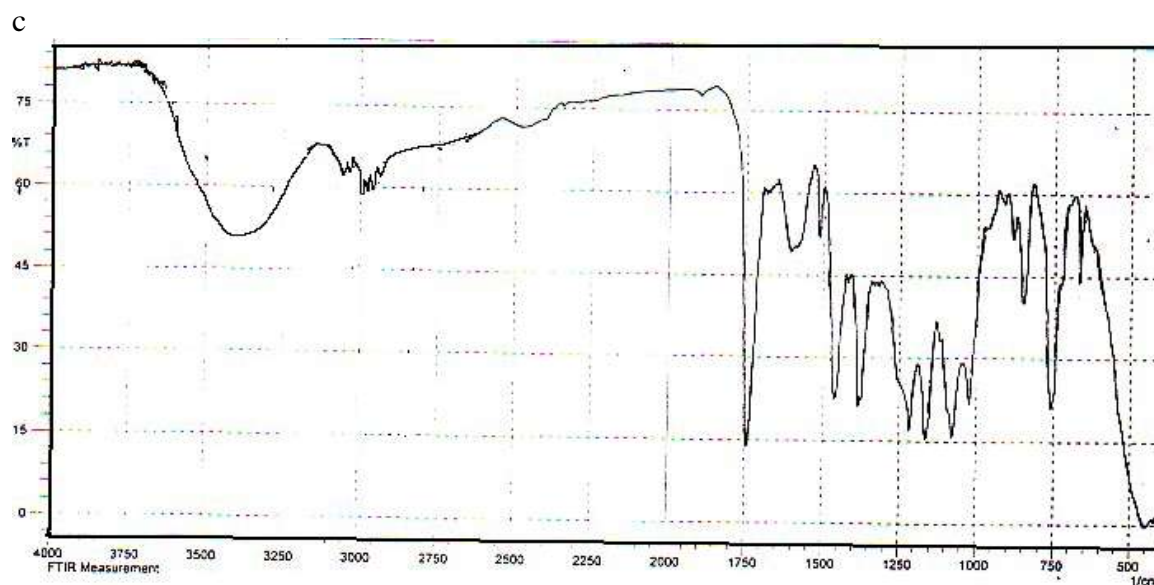
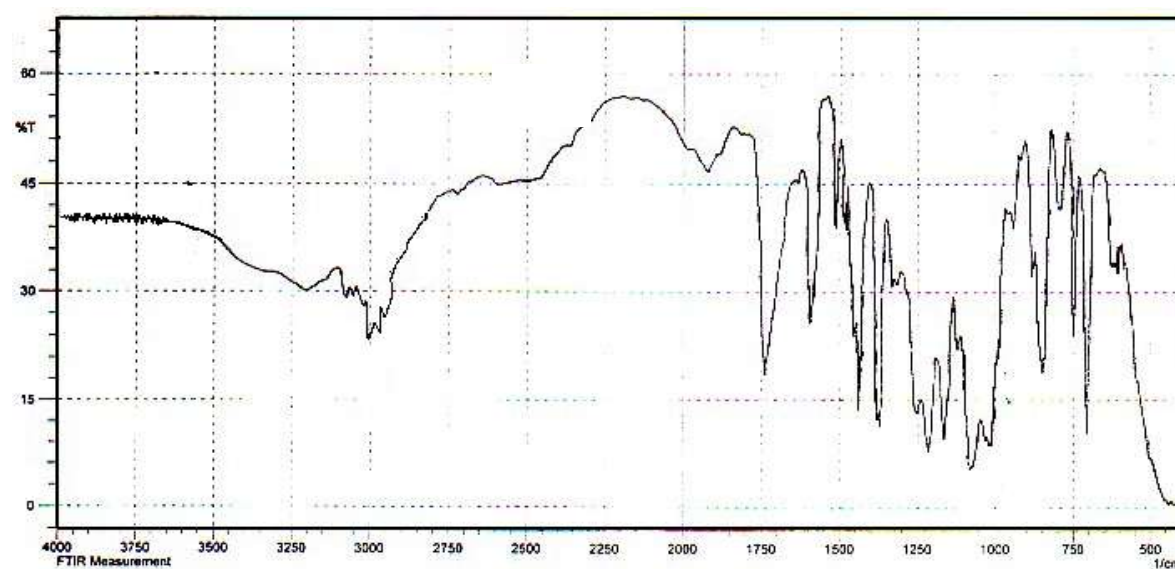


Figure / 1. FTIR spectra of a / □ ibuprofen (1) and b / ibuprofen chloride (2)



d

Figure / 2. FTIR spectra of c/□ compound (4), and d / compound (5).

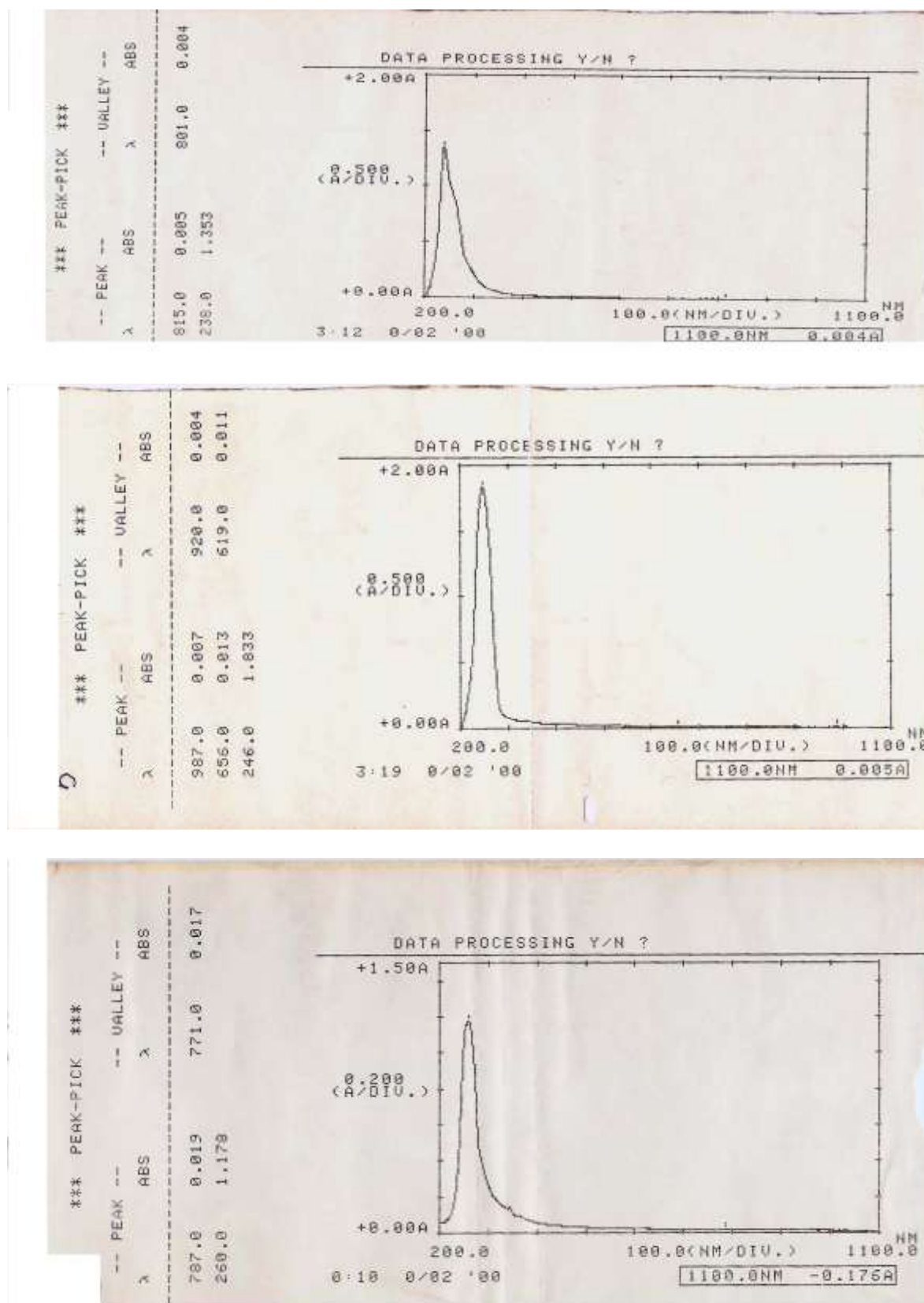


Figure / 3. UV spectra of compounds (2,4,5)

TABLE 1. Preparation and analytical data of compounds (2-5)

Comp. No	Molecular formula (Mr)	Rf	M.P C ⁰	Time h	Yield %	Solvent	FTIR V max/ cm ⁻¹	UV
3	C ₁₂ H ₂₀ O ₆ (260)	0.8	96	10	66	Acetone	3311, 2983, 1250 – 1050	291
2	C ₁₃ H ₁₈ OCl (225.5)	0.7	-	3	45.4	SOCl ₂	1800, 3040, 2950, 655	238
4	C ₂₅ H ₃₇ O ₆ (430)	0.61	-	24	33	Pyridin	3024, 2985, 1739, 1250-1050.	246
5	C ₁₉ H ₂₉ O ₆ (350)	0.5	-	3	50	CH ₂ Cl ₂	3380, 1740, 3024, 2985,	260

CONCLUSIONS

In this work fructose was used to synthesise a new carbohydrate ibuprofen ester (5) by esterification of its carboxylic acid group by one of the fructose hydroxyl groups . Preliminary results showed that the prepared fructose-drug conjugates underwent hydrolysis and released the pound ibuprofen and fructose. However, detailed kinetic studies of chemical and potential enzyme hydrolysis still remain to be done .

Acknowledgements

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